

REMARKS

As set forth above, the following amendments have been made to the application. A new section to set forth the cross references to related applications has been added at page 1. The diagram at page 11 has been deleted by amendment from that page and moved to the figures as new Figure 19. The diagram at pages 28 and 29 has been deleted by amendment from those pages and moved to the figures as Figure 20. The Brief Description of the Drawings section has been amended to refer to new Figures 19 and 20. Replacement pages 11, 28 and 29 and new Figures 19 and 20 are submitted herewith.

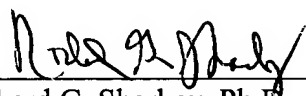
Claims 1-15 have been cancelled without prejudice. New Claims 16-19 have been added. Support for the new claims may be found, for example, in the following portions of the application: at page 47, lines 13-21 and page 50, lines 6-16, for claim 16; at page 50, line 9, for claim 17; at page 50, lines 17-20, for claim 18; and at page 50, lines 17-18 and 24, for claim 19.

No new matter has been added by these amendments.

The Director is authorized to charge any additional fees due by way of this Preliminary Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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Enclosures:

Replacement Pages 11, 28 and 29
Two Replacement Sheets with Figures 19 and 20

One method for reducing non-target tissue exposure to a diagnostic or therapeutic agent involves "pretargeting" the targeting moiety at a target site, and then subsequently administering a rapidly clearing diagnostic or therapeutic agent conjugate that is capable of binding to the "pretargeted" targeting moiety at the target site. A description of some embodiments of the pretargeting technique may be found in US Patent No. 4,863,713 (Goodwin et al.).

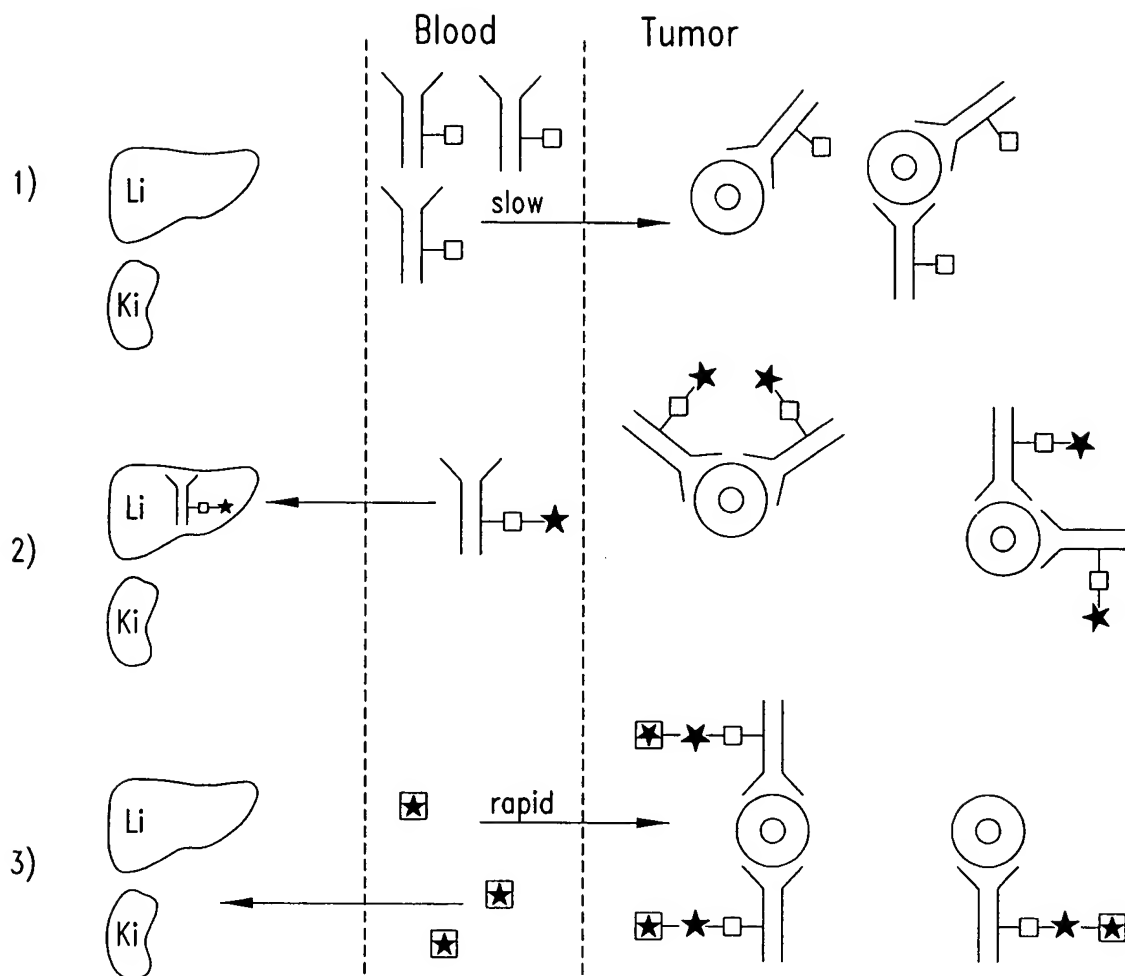
A typical pretargeting approach ("three-step") is schematically depicted in Figure 19.

conjugated to a therapeutic agent (e.g., radionuclide,
drug or anti-tumor agent) is undertaken. The
administered therapeutic agent-containing conjugate
binds to the previously localized targeting agent
5 containing conjugate. Therapeutic agent-containing
conjugate that does not bind at the target site will
be eliminated from the recipient's body at a much more
rapid rate than a monoclonal antibody-therapeutic
agent conjugate would be removed. Moreover, such
10 therapeutic agent-containing conjugates can be
chemically altered for more rapid excretion, if
necessary, to reduce non-target exposure to the
therapeutic agent.

A schematic of the administered components and
15 ultimate in vivo formed "sandwich" for a monoclonal
antibody-zinc finger protein/dsDNA-therapeutic agent
two-step pretargeting protocol are depicted in
Figure 20.

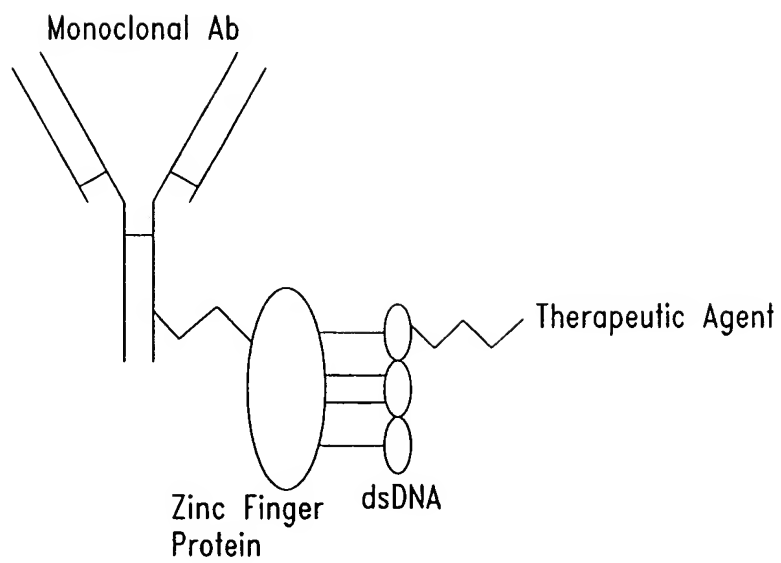
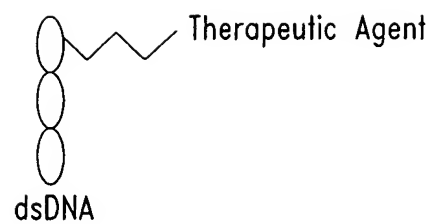
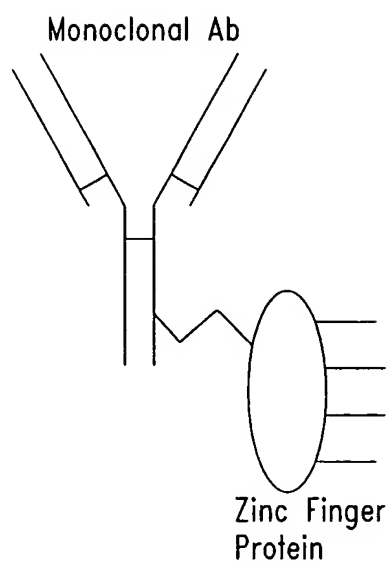
Use of the zinc finger protein/dsDNA fragment ligand/anti-ligand binding pair offers advantages with respect to immunogenicity. The targeting agent used in a pretargeting protocol may be human or humanized, and all of the other administered components (exclusive of the therapeutic agent) are human in origin. An additional advantage of this approach is that zinc finger proteins can be engineered to accommodate specific, high affinity interactions with synthetic or cloned dsDNA fragments, thereby eliminating non-specific interactions of the administered components with normal tissue.

One embodiment of this aspect of the present invention involves the use of pretargeting approaches to target double stranded DNA itself. Such protocols of the present invention are useful, for example, for gene therapy, delivery of tumor suppressive DNA, deleted genes and the like. More specifically, a targeting moiety-zinc finger protein is pretargeted to a target site. Subsequently, a dsDNA fragment that is complementary to the zinc finger protein is injected and allowed to bind to the localized zinc finger protein. Because zinc finger protein-DNA interaction is a normal cell physiologic mechanism, DNA will be delivered free of encumbering chemistry to the cellular milieu. The dsDNA is then internalized by



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Fig. 19



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Fig. 20